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EXAMINER	
HUYNH, PHUONG N	

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1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/760,362	CHEN, JAMES C.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,11,12,16-24,36 and 38-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,11,12,16-24,36 and 38-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/19/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-6, 11-12, 16-24, 36 and 38-56 are pending.

2. In view of the amendment filed 3/14/05, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-6, 11-12, 16-24, 36, 42, and 46-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of all conjugate comprising all photosensitizing compound, any photosensitizing compound such as "derivatives" of benzoporphyrin, bacteriochlorophyll, any chemical compound and any other agent conjugated to all targeting moiety wherein the targeting moiety is any ligand (first member of a binding pair), bindable to any receptor (second member of the binding pair), any antibody bindable to any antigen, and any antigen present on abnormal endothelium, any bispecific antibody construct further comprising any ligand and receptor component for a method to treat all neovascular disease of the eye, such as diabetic retinopathy, macular degeneration, and tumor as set forth in claims 1-6, 11-12, 16-24, 36, 42, and 46-49.

The specification discloses only a method to treat neovascular disease of the eye by administering a photosensitizing compound such as the ones listed on page 11 conjugated to a targeting moiety wherein the targeting moiety is selected from the group consisting of VEGF ligand, antibody or antibody fragment thereof that binds to the extracellular domain B (ED-B) of fibronectin, VEGF receptor, $\alpha 3\beta 3$ integrin, CEA antigen and bispecific antibody construct that is a combination of specific VEGF ligand and VEGF receptor on abnormal endothelium that lines or composes neovascular target tissue in the eye, allowing sufficient time, allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue; and illuminating the neovascular tissue with light having a wave length or waveband that matches the

excitation wave length or waveband of the photosensitizing compound wherein a combination of an intensity of light used for the step of illuminating and a duration of illumination is selected to produce a total fluence of irradiation such that the neovascular target tissue is destroyed and the non-target tissue through which the light passes remains undamaged wherein the photosensitized neovascular tissue is illuminated for a time interval of between about 4 minutes and 72 hours, or between about 60 minutes and 148 hours, or between about 2 minutes and 24 hours, and the total fluence of the light irradiation is from between about 30 Joules and about 25,000 Joules, or between about 100 Joules and about 20,000 Joules, or between about 500 Joules and about 10,000 Joules. The specification defines a photosensitizing compound is a any chemical compound that homes to a selected target and absorbs light but are *not limited to*, chlorins, bacteriochlorophylls, phthalocyanines, porphyrins, purpurins, merocyanines, psoralens, benzoporphyrin derivatives (BPD). Other compounds include indocyanine green (ICG); methylene blue; toluidine blue; texaphyrins; and *any other agent* that absorbs light in a range of 500 nm -1100 nm (page 11).

Other than the specific conjugate for the claimed method, there is insufficient guidance as to the structure of all conjugate comprising any and all photosensitizing compound, any photosensizing compound such as benzoporphyrin "derivative", any "other agent" that absorbs light in a range of 500 nm to 1100 nm conjugated to any and all targeting moiety, any targeting moiety that binds to any ligand, any receptor, any antigen and any bispecific antibody construct comprising any ligand and any receptor on the abnormal endothelium, the combination of intensity of light used and the duration of illumination for the total fluence of irradiation for the claimed method of treating any and all vascular disease of the eye, such as tumor of the eye, diabetic retinopathy, age-related macular degeneration.

With the exception of the specific conjugate for the claimed method, the specification does not adequately describe the genus of conjugate to be used by the claimed method. The exemplary embodiments nor the specification's general method appears to describe the structural features of photosensitizing compound and the structural features of the targeting moiety within the conjugate that are common to the genus. Further, the conjugate comprising verteporfin conjugated to antibody that binds to ED-B of fibronectin, bezoporphyrin derivative conjugated to VEGF (ligand) or antibody to CEA antigen, and texaphyrin conjugated to antibody that binds to $\alpha v\beta 3$ integrin do not appear to be a representative number of species within the genus for the claimed method. The specification provides no structural description of any photosensitizing compound, any photosensitizing compound such as "other agent" that absorbs light in a range of

500 nm-1100 nm. Other than the specific targeting moiety, the specification as filed provides no structure of any and all ligands, any receptors, any "agent" that function as a targeting agent to the abnormal endothelium for the claimed method. Without the structure of the photosensitizing compound and targeting moiety in the conjugate, the specification simply directs those skilled in the art to go figure out for themselves what the conjugate in the claimed method look like.

Further, there is inadequate written description about the method step wherein a combination of any intensity of light use for the step of illuminating and any duration of illumination such as at 4 minutes, at least 20 minutes, at least 1 hour and at least 24 hours along with any undisclosed target photosensitizing compound. In fact, the specification on page 10 discloses "both intensity and duration must be limited to ovoid over treating the subject". Given the lack of upper limit for the duration of illumination as set forth in claim 1 and 18-21, it is not clear if the claimed method as written is effective for treating neovascular disease without impairing or destroying other tissues. The recitation of "at least" 4 minutes (claim 18), "at least" 20 minutes (claim 19), "at least" 1 hour (claim 20) and "at least" 24 hours (claim 21) merely requires that lower limit of illumination be at least 4, 20, 1 and 24 hours, respectively. However, there is insufficient guidance for the intensity of the light used for the claimed method given the infinite number of undisclosed targeted photosensitizing compound in any combination of light intensity and duration of illumination.

For reasons indicated above, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 3/14/05 have been fully considered but are not found persuasive.

Applicants' position is that with respect to written description requirement, the examiner provides no evidence to support the examiner's position that photosensitizing compounds as a genus share any specific structural features in common. The specification provides a representative number of examples explicitly (17 by compound family, including porphyrins,

purpurin, chlorins, bacteriochlorophylls, phthalocyanines, merocyanines, psoralens, benzoporphyrin derivatives, porfimer sodium, δ-aminolevulinic acid, pyropheophorbides, texaphyrins, verteporfin, indocyanine green, methylene blue, and toluidine blue) and implicitly by defining the properties requisite for activity in photodynamic therapy. The specification also teaches as a targeting moiety the ED-B domain of fibronectin, an antibody specifically elicited to the ED-B domain of fibronectin, VEGF; a VEGF receptor', and an αvβ3 integrin receptor. The specification teaches that the intensity of light is selected to be sufficient for the light to reach the target tissue yet limited to avoid over-treating the subject (for example, see paragraph (038)). Thus, an upper limit for the intensity of light is selected so that no damage to non-target tissue occurs. The specification further discloses, for example, using an intensity of light substantially less that 500 mW/cm^2 and increasing the amount of time the target is exposed to the irradiation so that a greater amount of total energy or fluence may be used without increasing the amount of the intensity of the light used (see paragraph (050). The specification discloses that selection of a combination of a low intensity light and a prolonged duration of irradiation to activate the photosensitizer reduces the potential for damage to non-target tissue exposed to the irradiation. Contrary to the Examiner's assertion, there is an upper limit for the intensity of light used. The claimed subject matter requires a selection of a combination of an intensity of light used for the step of illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular target tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Thus, an upper limit for the intensity of light used it that which results in destruction of neovascular target tissue without damaging the non-target tissue through which the light passes. The specification teaches, for example, at paragraph (050), that a reduction in the intensity of light used is achieved by a concomitant increase in the duration of irradiation used.

In response, applicant appears to argue for enablement, the examiner's rejection is drawn to a written description. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. (See page 1115.) The specification as-filed discloses only the particular targeting agent conjugated to the particular photosensitizer for the claimed method (see above). The term "photosensitizing compound" as defined in the specification is any chemical compound which homes to one or more types of selected targeted cells and when contacted by radiation, any other agent that absorbs light in a range of 500 nm-1100nm (see page 10, [036]). However, the structure of any

photosensitizing compound such as "other agent" or any "chemical compound" conjugated to any targeting moiety that selectively binds to abnormal endothelium are not adequately described. Further, given the unlimited number of photosensitizing agent in the claimed method, the corresponding intensity of light, duration of illumination, and the corresponding total fluence of irradiation for the claimed method are not adequately described. The exemplary disclosure describes administering verteporfin conjugated to L19 antibody that binds to the ED-B of fibronectin to a subject, the subject is irradiated in one or more sessions for a total period of 10 minutes with 400 mW/cm2 of collimated LED light having a wavelength of 690nm for a total fluence of 240 Joules/cm2 (see example 1). The exemplary disclosure describes administering benzoporphyrin-anti-CEA antibody conjugate to a subject; the subject is irradiated for 1 hour with radiant of 250 mW/cm2 to provide a total fluence of 900 J/cm^2. As evidenced by the exemplary teachings that different conjugates of photosensitizing compound for different vascular diseases of the eye differ with respect to the combination of intensity of light used for the step of illuminating and duration of illumination for various photosensitizing compound, the method of treating a genus of neovascular disease using a genus of conjugate comprising a genus of photosensitizing compound such as methylene blue or toluidine blue where the combination with of intensity of light used and the duration of illumination to produce the total fluence of irradiation for the particular disease is not adequately described. In other words, the combination of an intensity of light used for the step of illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular target tissue is destroyed and the non-target tissue through which the light passes remains undamaged in the claimed method for all conjugate comprising various photosensitizing compound is not adequately described.

Applicant's argument with respect to alleged missing step on page 49 of the response is moot in view of the pending claims include as an element allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 3-6, 11-12, 17-21, 36, and 41-43 stand rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,756,541 (of record, May 1998; PTO 1449) as evident by Kramer *et al* (Ophthalmology 103(3): 427-38, March 1996; PTO 892).

The '541 patent teaches a method to treat neovascular disease of the eye such as age-related macular degeneration comprising administering a conjugate comprising photosensitizing compound such as chlorine and green porphyrin (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular) coupled to a specific binding ligand such as antibody that binds to the target ocular tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular) or low density lipoprotein ligand that binds to the LDL receptor on the abnormal endothelium (See col. 3, lines 42-48, in particular), allowing sufficient time after administering the reference conjugate to permit the binding of the conjugate the to the specific ocular tissue being targeted such as about 1 minute to about 2 hours (See col. 4, line 65 bridging col. 5, lines 1-4, claim 3 of '541 patent, in particular) which inherently also allows non-specifically bound conjugate to clear from non-target tissue, and illuminating the neovascular tissue with light from a coherent Argon dye laser (See col. 5, lines 45-50, in particular) that corresponds with the wavelength of the photosensitizing agent such as between about 550 and 695 nm (See col. 4, lines 35-45, in particular) for a period such as 90-270 seconds to activate the reference photosensitized compound wherein the neovascular tissue is treated with a total fluence of light irradiation from 50 J/cm 2 to 150 J/cm^2 (See col. 5, lines 5-8, claim 2 of '541 patent, in particular) for a duration such as 90-270 seconds of irradiation (See col. 5, lines 5-8, in particular). The reference method wherein the neovascular tissue is choroidal vessels (See col. 1, lines 28, col. 2, line 1-2, in particular). The reference method further comprises the step of illuminating the neovasculature tissue with laser light for a period of time such as 90 second to cause damage to the neovasculature tissue without impairing or destroying other tissue (See column 5, lines 10-12 and lines 21, claims of '541 patent, in particular). The reference method wherein the reference targeted photosensitizing compound is formulated in liposome (See col. 3, line 40, in particular). Claim 18 is included in this rejection because the reference method wherein the photosensitized neovascular tissue is illuminated for 270 seconds (See col. 5, line 7-8, in particular) which is equivalent to at least 4 minutes. Claims 19-21 are included in this rejection because the '541 patent teaches the various parameters used for effective selective photodynamic therapy are interrelated and should be adjusted to produce significant enhancement of visual acuity without significant damage to the eye tissue (See col. 4, lines 22-30, in particular). Claim 36 is included

in this rejection because the instruction to a person to conduct the claimed method at the time the invention was made is within the teachings of the '541 patent. Claim 43 is included in this because verteporfin is a generic name as evident by the teaching of Kramer et al (abstract, in particular) for benzoporphyrin derivative monoacid ring A, BPD-MA as taught by the '541 patent (See col. 1, line 44-45, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 3/14/05 have been fully considered but are not found persuasive.

Applicants' position is that (1) Strong et al. does not disclose selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to achieve target tissue destruction without damage to non-targeted tissue through which the light passes (see page 56 of argument). (2) Strong et al discloses that its method results in deleterious effects of the tissue immediately surrounding the activated photosensitizer, making no distinction between target and non-targeted tissue and discloses that mild retina whitening occurs (See col. 2, lines 31-33 and col. 5, lines 10-13). (3) Strong et al ('541 patent) does not teach diabetic retinopathy.

In contrast to applicant's assertion that the reference does not disclose a method to treat neovascular disease of the eye that includes allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue, the '541 patent teaches a method to treat neovascular disease of the eye such as macular degeneration that includes allowing sufficient time after administering the reference conjugate to permit the binding of the conjugate the to the specific ocular tissue being targeted such as about 1 minute to about 2 hours (See col. 4, line 65 bridging col. 5, lines 1-4, claim 3 of '541 patent, in particular). The reference step inherently allows non-specifically bound conjugate to clear from non-target tissue such that without damage to the eye tissue. Claim 1 does not recite the particular intensity of light in combination of the particular duration of illumination.

In response to applicant's argument that Strong et al discloses a method that results in deleterious effects of the tissue immediately surrounding the activated photosensitizer. There is no evidence in the specification as filed that the claimed method differs from the method of Strong et al, i.e. the neovasuclar tissue is destroyed and the non-target tissue throughout which the light passes remains undamaged.

In contrast to applicant's assertion that Strong et al does not disclose selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to achieve target tissue destruction without damage to non-target tissue, the '541 patent teaches that the reference method illuminates the neovascular tissue with light from a coherent Argon dye laser (See col. 5, lines 45-50, in particular) that corresponds with the wavelength of the photosensitizing agent such as between about 550 and 695 nm (See col. 4, lines 35-45, in particular) for a period to activate the reference photosensitized compound wherein the neovascular tissue is treated with a total fluence of light irradiation from 50 J/cm 2 to 150 J/cm^2 (See col. 5, lines 5-8, claim 2 of '541 patent, in particular) for a duration such as 90-270 seconds of irradiation (See col. 5, lines 5-8, in particular). The '541 patent teaches the various parameters used for effective selective photodynamic therapy are interrelated and should be adjusted to produce significant enhancement of visual acuity without significant damage to the eye tissue (See col. 4, lines 22-30, in particular).

In contrast to applicant's assertion that Strong et al ('541 patent) does not teach treating diabetic retinopathy, the '541 patent teaches a method of treating neovascular diseases of the eye such as age-related muscular degeneration (see col. 1, lines 1-23, col. 6, lines 61-65, in particular). As evidenced by the definition of instant specification, neovascular diseases of the eye include diabetic retinopathy, age-related macular degeneration (see page 1, [002], page 2 [004] of instant specification). Neovascular diseases of the eyes share a common underlying etiology (see argument, page 23).

In response to applicant's argument that Strong et al discloses that its method results in deleterious effects of the tissue immediately surrounding the activated photosensitizer, making no distinction between target and non-targeted tissue and discloses that mild retina whitening occurs, the claimed method as recited in claim 1 is not different than the method of '541 patent because the specific wavelength, the duration and total fluence are not recited in the claim 1.

7. Claims 1, 3-6, 11, 18, 36, 42-43 and 45 stand rejected under 35 U.S.C. 102(b) as being anticipated by Kramer *et al* (Ophthalmology 103(3): 427-38, March 1996; PTO 892).

Kramer *et al* teach a method of treating unwanted choroidal neovasculature (CNV) such as diabetic retinopathy, age-related macular degeneration, corneal neovascularization and ocular tumor (See entire document, page 437, in particular) by administering to a mammal such as monkeys a photosensitizing compound such as benzoporphyrin derivative (BDP) or verteporfin

conjugated to a targeting moiety such as liposome or LDL that selectively binds to LDL receptor and accumulate in rapidly proliferating endothelium of the eye (See page 428, col. 1, par. 2-3, in particular), allowing sufficient time such as 10, 20, 30, 40, 50, 60 and 80 minutes after dye injection to permit the non-specific bound conjugate to clear from non-target tissue (See page 433, col. 1, page 435, col. 2, last par., in particular) and illuminating the neovascular tissue with light at a wavelength such as 692 nm (see page 429, col. 1, par. 2, in particular) that matches the light absorption wavelength (see page 428, col. 1, par. 3, in particular) for a duration such as 4 minutes 9 second which is at least 4 minutes (see page 437, col. 1, in particular) at an intensity or fluence of 150 J/cm^2 which is between about 30 J/cm^2 to about 25,000 J/cm^2 (see page 437, col. 1, in particular). The reference method wherein the light is coherent laser light (See page 429, Photodynamic Therapy, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 3/14/05 have been fully considered but are not found persuasive.

Applicants' position is that Kramer et al. does not disclose selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to achieve target tissue destruction without damage to non-targeted tissue through which the light passes. Kramer et al discloses that is method results in damage of both inner and outer retina, and that treatments of normal retina and choroids using its methods resulted in damage graded 1 to 3.

In response to applicant's argument that Kramer does not disclose selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to achieve target tissue destruction without damage to non-targeted tissue through which the light passes, Kramer *et al* teach a method of treating unwanted choroidal neovasculature (CNV) such as diabetic retinopathy, age-related macular degeneration, corneal neovascularization and ocular tumor (See entire document, page 437, in particular) by administering to a mammal such as monkeys a photosensitizing compound such as benzoporphyrin derivative (BDP) or verteporfin conjugated to a targeting moiety such as liposome or LDL that selectively binds to LDL receptor and accumulate in rapidly proliferating endothelium of the eye (See page 428, col. 1, par. 2-3, in particular), allowing sufficient time such as 10, 20, 30, 40, 50, 60 and 80 minutes after dye injection to permit the non-specific bound conjugate to clear from non-target tissue (See page 433, col. 1, page 435, col. 2, last par., in particular) and illuminating the neovascular tissue with light at a wavelength such as 692 nm (see

page 429, col. 1, par. 2, in particular) that matches the light absorption wavelength (see page 428, col. 1, par. 3, in particular) for a duration such as 4 minutes 9 second which is at least 4 minutes (see page 437, col. 1, in particular) at an intensity or fluence of 150 J/cm^2 which is between about 30 J/cm^2 to about 25,000 J/cm^2 (see page 437, col. 1, in particular). Claim 1 merely requires any photosensitizing compound conjugate. Kramer et al teach the claimed photosensitizing compound conjugate for the claimed method.

In response to applicant's argument that Kramer et al discloses that is method results in damage of both inner and outer retina, and that treatments of normal retina and choroids using its methods resulted in damage graded 1 to 3, the claimed method uses the same photosensitizing compound conjugate as taught by the reference, the reference compound is inherently has the same effect as the claimed method. Further, there is no evidence in the specification as filed that the claimed method differs from the teachings of Kramer et al.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1, 2, 11 and 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,756,541 (of record, May 1998; PTO 1449) as evident by Kramer *et al* (Ophthalmology 103(3): 427-38, March 1996; PTO 892) in view of Klyashchitsky *et al* (or record, J of Controlled Release 29(1-2): 16-16, 1994; PTO 892) and Boulton *et al* (of record, Br J Opthlalmol 82: 561-568, 1998; PTO 892), Blaauwgeers *et al* (of record, Am J Pathology 155(2): 421-428, 1999; PTO 892), or Prewett *et al* (of record, Cancer Res 59: 5209-18, 1999; PTO 892).

The teachings of the '541 patent as evident by Kramer *et al* have been discussed supra.

The claimed invention in claim 2 differs from the teachings of the references only that the method wherein the light is non-laser light.

The claimed invention in claim 11 differs from the teachings of the references only in that the method wherein the targeting moiety is an VEGF (first member) bindable to a VEGF receptor.

The claimed invention in claim 38 differs from the teachings of the references only that the targeted photosensitizing compound is conjugated to an antibody that binds to a VEGF receptor.

The claimed invention in claim 39 differs from the teachings of the reference only that the targeted photosensitizing compound is conjugated to VEGF.

The claimed invention in claim 40 differs from the teachings of the reference only that the targeted photosensitizing compound is conjugated to VEGF receptor.

Klyashchitsky *et al* teach photodynamic therapy (PDT) is based on the ability of porphyrins and other photosensitizers to be accumulated preferentially in cells such as tumors and to generate singlet oxygen when activated by visible light (See abstract, in particular). Klyashchitsky *et al* further teach that targeting molecule such as antibody that is specific for antigen or the receptor on neovascular disease such as tumor is efficient and useful for delivery of PDT selectively to the tumor cells (See abstract, in particular).

Boulton *et al* teach VEGF plays a role in neovascularization in diabetic retinopathy and antibody to VEGF detects VEGF in endothelial cell in the retinal or choroidal of diabetic retina (see Abstract, Table 1, page 563, column 1, first paragraph, in particular). Boulton *et al* teach VEGF binds to VEGF receptors on endothelial cells such as inner retina (See page 566, column 2, first full paragraph, in particular).

Blaauwgeers *et al* teach VEGF receptor such as VEGFR-2 or KDR and VEGFR-3 (flt-4) are localized to the choriodal capillaries (CC) endothelium facing the retinal pigment epithelium layer whereas VEGFR-1 is found in the inner CC on other choroidal vessel (See abstract, in particular). Blaauwgeers *et al* teach that unregulated VEGF secretion by RPE plays a role in neovascularization.

Prewett *et al* teach antibody such as DC101 that binds specifically to Flk-1/KDR VEGF receptor and the reference antibody is useful for inhibits angiogenesis (See entire document, abstract, Fir 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody that binds to the target ocular tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular) or LDL that is conjugated to the photosensitizing compound as taught by the '541 patent for the VEGF that plays a role in neovascularization in diabetic retinopathy as taught by Boulton *et al,* or the antibody to the VEGF receptor as taught by Prewett *et al* or the VEGF receptor as taught by Blaauwgeers *et al* for a method to treat

neovascular disease by targeting the photosensitizing compound to treat neovascular disease as taught by the '541 patent and Klyashchitsky *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Klyashchitsky *et al* teach that targeting molecule such as antibody that is specific for antigen or receptor is efficient and useful for selective delivery of PDT to the site of interest (See abstract, in particular). Prewett *et al* teach antibody such as DC101 that binds specifically to the Flk-1/KDR VEGF receptor and is useful for inhibiting angiogenesis or neovascularization (See entire document, abstract, Fir 2, in particular). Blaauwgeers *et al* teach VEGF receptor such as VEGFR-2 or KDR and VEGFR-3 (flt-4) are localized to the choriodcapillaries (CC) endothelium facing the retinal pigment epithelium layer whereas VEGFR-1 is found in the inner CC on other choroidal vessel (See abstract, in particular). Boulton *et al* teach that VEGF binds to VEGF receptors on endothelial cells such as inner retina play a role in neovascularization in diabetic retinopathy (See page 566, column 2, first full paragraph, abstract, in particular). The '541 patent teaches that administering a photosensitizing compound such as chlorine and green porphyrin (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular) coupled to a specific binding ligand such as antibody that binds to the target ocular tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular) is useful for treating neovascular disease of the eye such as age-related macular degeneration (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular).

Applicants' arguments filed 3/14/05 have been fully considered but are not found persuasive.

Applicants' position is that (1) strong et al are discussed above. (2) Boulton et al does not teach or suggest a conjugate that includes a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium. Boulton et al does not disclose allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue. (3) Blaauwgeers et al does not teach or suggest treating neovascular disease using a photosensitizing compound nor does the reference teach or suggest a conjugate that include a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium. (4) Thus, combining the teachings of Blaauwgeers et al with Strong et al. or with the combination of Strong et al. and Boulton et al. does not teach or suggest selecting a

combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. Hence, even if, arguendo, Blaauwgeers et al. teaches that the loss of polarity of VEGF production may play a role in the pathogenesis of choroidal neovascularization, the combination of the teachings of Blaauwgeers et al with Strong et al. or with the combined teachings of Strong et al. and Boulton et al. does not teach or suggest every element of claim 1 and its dependent claims. (5) Klyashchitsky et al. does not teach or suggest treating neovascular disease using a photosensitizing compound, nor does the reference teach or suggest a conjugate that includes a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium. (6) Klyashchitsky et al. does not disclose allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue. Klyashchitsky et al does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. (7) Prewett et al. does not teach or suggest treating neovascular disease using a photosensitizing compound, nor does the reference teach or suggest a conjugate that includes a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium. (8) Prewett el al does not disclose allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue. Prewett et al. does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. (9) The combined teachings of the Strong et al with the teachings of Boulton et al, Blaauwgeers et al., Klyashchitsky et al. and Prewett et al. does not result in the instantly claimed methods.

In contrast to applicants assertion that the combined teachings of the Strong et al with the teachings of Boulton et al, Blaauwgeers et al., Klyashchitsky et al. and Prewett et al. does not result in the instantly claimed methods, the teachings of the '541 patent as evident by Kramer *et al* teach the combination of intensity of light used for the step of illuminating and a duration of illumination to produce a total fluence of irradiation, the '541 patent teaches a method to treat neovascular disease of the eye such as age-related macular degeneration comprising administering a conjugate comprising photosensitizing compound such as chlorine and green porphyrin (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular) coupled to

a specific binding ligand such as antibody that binds to the target ocular tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular) or low density lipoprotein ligand that binds to the LDL receptor on the abnormal endothelium (See col. 3, lines 42-48, in particular), allowing sufficient time after administering the reference conjugate to permit the binding of the conjugate the to the specific ocular tissue being targeted such as about 1 minute to about 2 hours (See col. 4, line 65 bridging col. 5, lines 1-4, claim 3 of '541 patent, in particular) which inherently also allows non-specifically bound conjugate to clear from non-target tissue, and illuminating the neovascular tissue with light from a coherent Argon dye laser (See col. 5, lines 45-50, in particular) that corresponds with the wavelength of the photosensitizing agent such as between about 550 and 695 nm (See col. 4, lines 35-45, in particular) for a period such as 90-270 seconds to activate the reference photosensitized compound wherein the neovascular tissue is treated with a total fluence of light irradiation from 50 J/cm 2 to 150 J/cm^2 (See col. 5, lines 5-8, claim 2 of '541 patent, in particular) for a duration such as 90-270 seconds of irradiation (See col. 5, lines 5-8, in particular).

The claimed invention in claim 2 differs from the teachings of the references only that the method wherein the light is non-laser light.

The claimed invention in claim 11 differs from the teachings of the references only in that the method wherein the targeting moiety is an VEGF (first member) bindable to a VEGF receptor.

The claimed invention in claim 38 differs from the teachings of the references only that the targeted photosensitizing compound is conjugated to an antibody that binds to a VEGF receptor.

The claimed invention in claim 39 differs from the teachings of the reference only that the targeted photosensitizing compound is conjugated to VEGF.

The claimed invention in claim 40 differs from the teachings of the reference only that the targeted photosensitizing compound is conjugated to VEGF receptor.

Klyashchitsky *et al* teach photodynamic therapy (PDT) is based on the ability of porphyrins and other photosensitizers to be accumulated preferentially in cells such as tumors and to generate singlet oxygen when activated by visible light (See abstract, in particular). Klyashchitsky *et al* further teach that targeting molecule such as antibody that is specific for antigen or the receptor on neovascular disease such as tumor is efficient and useful for delivery of PDT selectively to the tumor cells (See abstract, in particular).

The Boulton *et al* reference is cited for the teachings of targeting moiety such as VEGF that plays a role in neovascularization in diabetic retinopathy, antibody that binds to VEGF that is found in endothelial cell in the retinal or choroidal of diabetic retina (see Abstract, Table 1, page 563, column 1, first paragraph, in particular). Boulton *et al* teach VEGF binds to VEGF receptors on endothelial cells such as inner retina (See page 566, column 2, first full paragraph, in particular).

Blaauwgeers *et al* teach VEGF receptor such as VEGFR-2 or KDR and VEGFR-3 (flt-4) are localized to the choriodal capillaries (CC) endothelium facing the retinal pigment epithelium layer whereas VEGFR-1 is found in the inner CC on other choroidal vessel (See abstract, in particular). Blaauwgeers *et al* teach that unregulated VEGF secretion by RPE plays a role in neovascularization.

Prewett *et al* teach antibody such as DC101 that binds specifically to Flk-1/KDR VEGF receptor and the reference antibody is useful for inhibits angiogenesis (See entire document, abstract, Fir 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the targeting moiety in the conjugate such as antibody that binds to the target ocular tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular) or LDL that is conjugated to the photosensitizing compound as taught by the '541 patent for the VEGF that plays a role in neovascularization in diabetic retinopathy as taught by Boulton *et al,* or the antibody to the VEGF receptor as taught by Prewett *et al* or the VEGF receptor as taught by Blaauwgeers *et al* for a method to treat neovascular disease by targeting the photosensitizing compound to treat neovascular disease as taught by the '541 patent and Klyashchitsky *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Klyashchitsky *et al* teach that targeting molecule such as antibody that is specific for antigen or receptor is efficient and useful for selective delivery of PDT to the site of interest (See abstract, in particular). Prewett *et al* teach antibody such as DC101 that binds specifically to the Flk-1/KDR VEGF receptor and is useful for inhibiting angiogenesis or neovascularization (See entire document, abstract, Fir 2, in particular). Blaauwgeers *et al* teach VEGF receptor such as VEGFR-2 or KDR and VEGFR-3 (flt-4) are localized to the choriodcapillaries (CC) endothelium facing the retinal pigment epithelium layer whereas VEGFR-1 is found in the inner CC on other

choroidal vessel (See abstract, in particular). Boulton *et al* teach that VEGF binds to VEGF receptors on endothelial cells such as inner retina play a role in neovascularization in diabetic retinopathy (See page 566, column 2, first full paragraph, abstract, in particular). The '541 patent teaches that administering a photosensitizing compound such as chlorine and green porphyrin (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular) coupled to a specific binding ligand such as antibody that binds to the target ocular tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular) is useful for treating neovascular disease of the eye such as age-related macular degeneration (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular).

10. Claims 1, 11, and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,756,541 (of record, May 1998; PTO 1449) as evident by Kramer *et al* (Ophthalmology 103(3): 427-38, March 1996; PTO 892) in view of US Pat 6,270,749 B1 (filed June 10, 1999; PTO 892).

The teachings of the '541 patent as evident by Kramer *et al* have been discussed supra.

The claimed invention in claim 11 differs from the teachings of the references only in that the method wherein the targeting moiety is an antibody bindable to an antigen such as VEGF present on abnormal endothelium.

The claimed invention in claim 43 differs from the teachings of the references only in that the method to treat neovascular disease wherein the photosensitizing compound is texaphyrin.

The '749 patent teaches a method of treating unwanted choroidal neovasculature such as aged related macular degeneration (See abstract, col. 6, lines 25-42, col. 23, lines 10-11, in particular) comprising administering to the mammal an effective amount of a conjugate comprising a photosensitizing compound such as lutetium texaphyrin or LuT2BET, or benzoporphyrin derivatives (See col. 2, lines 65-70, in particular) conjugated to a targeting moiety such as a monoclonal antibody to VEGF on abnormal endothelium (See col. 10, lines 48-50, col. 19, lines 30-45, in particular) and irradiating the choroidal neovasculature with laser light (see col. 21, lines 5-8, in particular) such that the light is occlude the choroidal neovasculature (See col. 25, line 31, in particular). The advantage of the reference method is that the reference PDT treatment is more selective over other technique such as photocoagulation (See col. 25, lines 35-37, in particular). The advantages of texaphyrins are that it is more versatile for use in humans

as compared to porphyrins (See abstract, in particular), texaphyrins are cleared quickly from the body and no toxicity to the eye has been observed (See col. 5, lines 8-16, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the photosensitizing compound such as chlorine and green porphyrin in the conjugate as taught by the '541 for the photosensitizing compound such as texaphyrin as taught by the '749 patent for a method to treat neovascular disease such as macular degeneration as taught by the '541 patent and the '749 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to substitute the chlorine and green porphyrin in the conjugate because the '749 patent teaches that the advantages of texaphyrins are that it is more versatile for use in humans as compared to porphyrins (See abstract, in particular), and texaphyrins are cleared quickly from the body and no toxicity to the eye has been observed (See col. 5, lines 8-16, in particular).

Applicants' arguments filed 3/14/05 have been fully considered but are not found persuasive.

Applicants' position is that (1) strong et al are discussed above. (2) Kramer et al. does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. (3) Neither Strong et al. nor Blumenkranz et al (the'749 patent) alone or in combination, teaches or suggests selecting a combination of intensity of light used for irradiating and a duration of irradiation to produce a total fluence of the light sufficient to activate the photosensitizer compound such that the target tissue is destroyed and the healthy non-target tissue remains undamaged.

In response, neither applicant has shown the combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged in the specification as filed. The teachings of Strong et al and Blumenkranz et al have been discussed supra and are incorporated here by reference.

11. Claims 1, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,756,541 (of record, May 1998; PTO 1449) as evident by Kramer *et al* (Ophthalmology 103(3): 427-38, March 1996; PTO 892) in view of WO 97/31582 (September 4, 1997; PTO 1449).

The teachings of the '541 patent as evident by Kramer et al have been discussed supra.

The claimed invention in claim 44 differs from the teachings of the references only in that the method to treat neovascular disease wherein the photosensitizing compound is indocyanine green.

The WO 97/31582 publication teaches a photosensitizing compound such as indocyanine green for photodynamic therapy in treating neovascular disease such as tumor or induction of photocoagulation (See entire document, page 1-2, in particular). The indocyanine dye (ICG) has been use in humans (page 1 in particular), and effective to destroyed the irradiated tissue and eliminating proliferating cancer cells without induce scarring, and other adverse conditions (See summary of invention, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the photosensitizing compound such as chlorine and green porphyrin in the conjugate as taught by the '541 for the indocyanine green as taught by the WO 97/31582 publication for a method to treat neovascular disease such as macular degeneration as taught by the '541 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to substitute the chlorine and green porphyrin in the conjugate because the WO 97/31582 publication teaches that the indocyanine dye (ICG) has been use in humans (page 1 in particular), and effective to destroyed the irradiated tissue and eliminating proliferating cancer cells without induce scarring, and other adverse conditions (See summary of invention, in particular).

Applicants' arguments filed 3/14/05 have been fully considered but are not found persuasive.

Applicants' position is that (1) strong et al are discussed above. (2) Abels et al. does not teach or suggest selecting a combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged. (3) Neither Strong et al. nor Abels et al, alone or in combination, teaches or suggests selecting a combination of

intensity of light used for irradiating and a duration of irradiation to produce a total fluence of the light sufficient to activate the photosensitizer compound such that the target tissue is destroyed and the healthy non-target tissue remains undamaged.

In response, neither applicant has shown the combination of an intensity of light for illuminating and a duration of illumination to produce a total fluence of irradiation such that the neovascular tissue is destroyed and the non-target tissue through which the light passes remains undamaged in the specification as filed. The teachings of Strong et al and Abels et al (the WO 97/731582 publication) have been discussed supra and are incorporated here by reference.

12. The following new grounds of rejections are necessitated by the amendment filed 3/14/05.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 52-56 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "αvβ3 integrin, the extra-domain B of fibronectin" in Claim 52 represents a departure from the specification and the claims as originally filed. The specification discloses *antibody and antibody fragment* that bind to VEGF receptor, αvβ3 integrin, and the extra-domain B of fibronectin (see specification page 12, lines 1-9). The specification does not disclose "αvβ3 integrin, and the extra-domain B of fibronectin as the targeting moiety in the conjugate for the claimed method. Amending claim 52 as suggested above would obviate this rejection.

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

16. Claim 52 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "antibody L19" in claim 52 is ambiguous and indefinite because "L19" is merely a laboratory designation which does not clearly define the product in the claimed method, since different laboratories may use the same laboratory designation to define completely distinct antibody. Amending claim 52 to recite "an human antibody or binding fragment thereof that binds specifically to the extra-domain B of fibronectin" would obviate this rejection.

17. Claims 52-56 are free of prior art and would be allowable if amended as suggested above.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

20. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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